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TITLE: A Light Weight, Portable EPR Spectrometer for Tissue Oxygenation Measurement

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13. ABSTRACT (Maximum 200 words)

The aim of this project is to provide a reliable means to obtain fast, accurate, and repeated measurements of pO2, perfusion, pH, and potentially, nitric oxide (NO) directly in tissues in patients in the LSTAT (Life Support for Trauma and Transport) system in order to monitor their status and provide data for their active management. Our approach exploits the capabilities of in vivo EPR techniques to make such measurements. In Phase I we initiated the design studies for adapting our existing technology to a portable configuration and started the construction of a key component for the proposed use: the catheter/needle probe which will enable us to make the desired measurements at various depths as required for this use, using an EPR frequency of 0.5 to 1.2 GHz. During Phase II we will complete the design and then construct a spectrometer suitable for the described purposes. We also will adapt the existing techniques for measuring pO2, pH, effective perfusion, and NO, to the needs and constraints for making these measurements in patients within the LSTAT system.

14. SUBJECT TERMS
Oxygen, Needle/Cathetor, Paramagnetic, Resonance, Probe, Spectrometer, Portable, LSTAT

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Peter D. Kanmaier 5 oktober 1992

PI - Signature Date

Table of Contents

1. Identification and Significance of the Problem.

The goal of this proposal is to develop components and equipments for a **Low Cost Portable Electron Paramagnetic Resonance Spectrometer**. The main application of the instrument is for the determination of tissue oxygenation. Our approach will provide accurate, reliable and sensitive measurements of the partial pressure of oxygen (p02) in deep muscle and skin (and other sites as well) with a portability that will be compatible with health care systems and battlefield conditions. The technique will require that injection of the sensing materials (inert carbon based materials such as India ink for which there already is extensive experience on its long term stability and safety in human tissues) into the sites to be measured. The injections can be made by very small needles and will provide a means to obtain localization of the measurements that will be individualized to fit the measurement needs of each potential patient. Measurements can be made in seconds and repeated as often as desired.

The output of the device will be simple to interpret and fully compatible with the integration into standard computer and data storage devices. The instrument can be very rugged, involving only components with very high reliability and simple yet rigid construction.

The proposed Electron Paramagnetic Resonance (EPR) technology appears to be superior to any existing methods to make such measurements from both the surface and deeper tissues. The standard method to measure p02 in tissues is the Clark electrode but this requires an injection of a needle for each measurement and the technology is noteworthy fragile and the sensitivity is very limited. The only optical methods that appear potentially useful for such a device are those based on Near InfraRed(NIR) measurements. They report principally on hemoglobin rather than tissue p02, have limited sensitivity and cannot provide precisely localized measurements. This would, however,
appear to be an area in which positive technical developments could occur.

Nuclear Magnetic Resonance (NMR) techniques, in theory, provides another means of non-invasive measurement of p02 but so far it has provided only limited and indirect data with low sensitivity. Perhaps most fundamentally limiting, however, is the difficulty in making a portable NMR system.

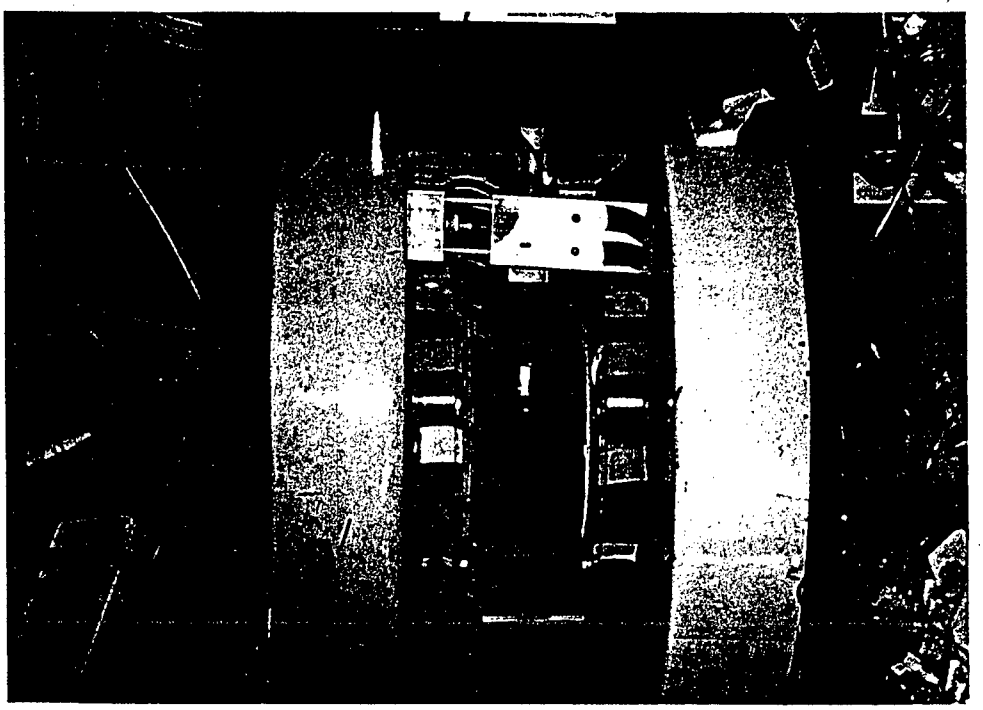
A proto-type EPR spectrometer has been developed at Dartmouth Medical College and it is shown in Fig. 1. The schematic of the spectrometer is shown in Fig. 2. The existing instrument already provides very satisfactory measurements of p02 in tissues in awake animals but is not portable.

The technical features of the existing instrument include:

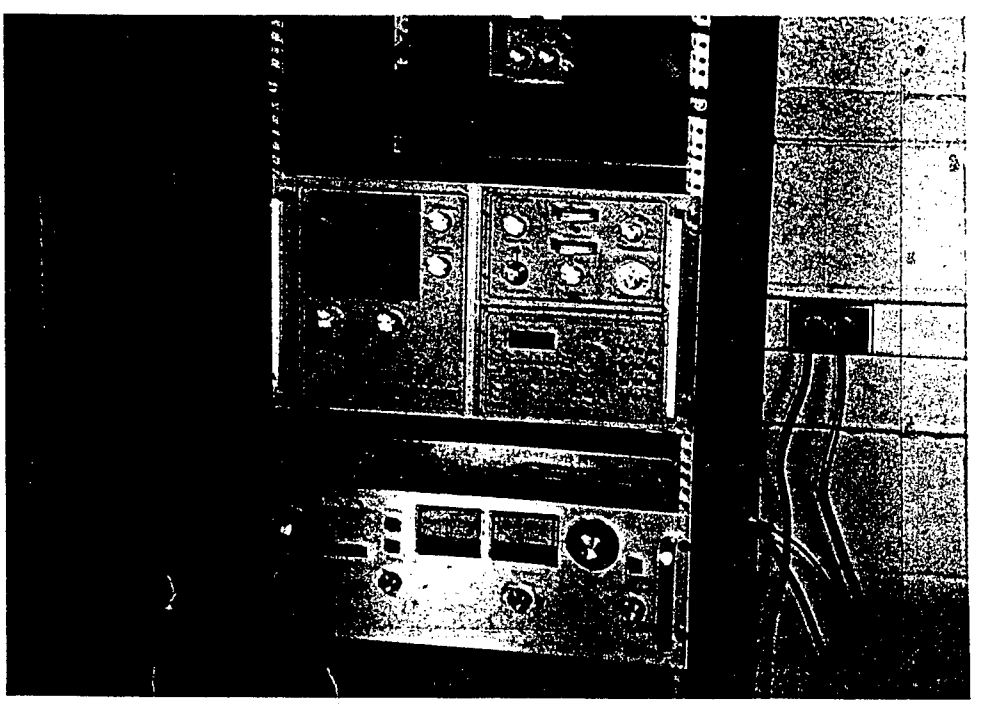
1. The use of 1 GHz EPR with a consequent depth of sensitivity of up to 10mm under most circumstances, and of several inches with the use of a needle probe.

2. The use of spatially resolved high resolution spectroscopy to obtain the data on p02 .

Fig. 1 Photograph of Existing EPR Spectrometer

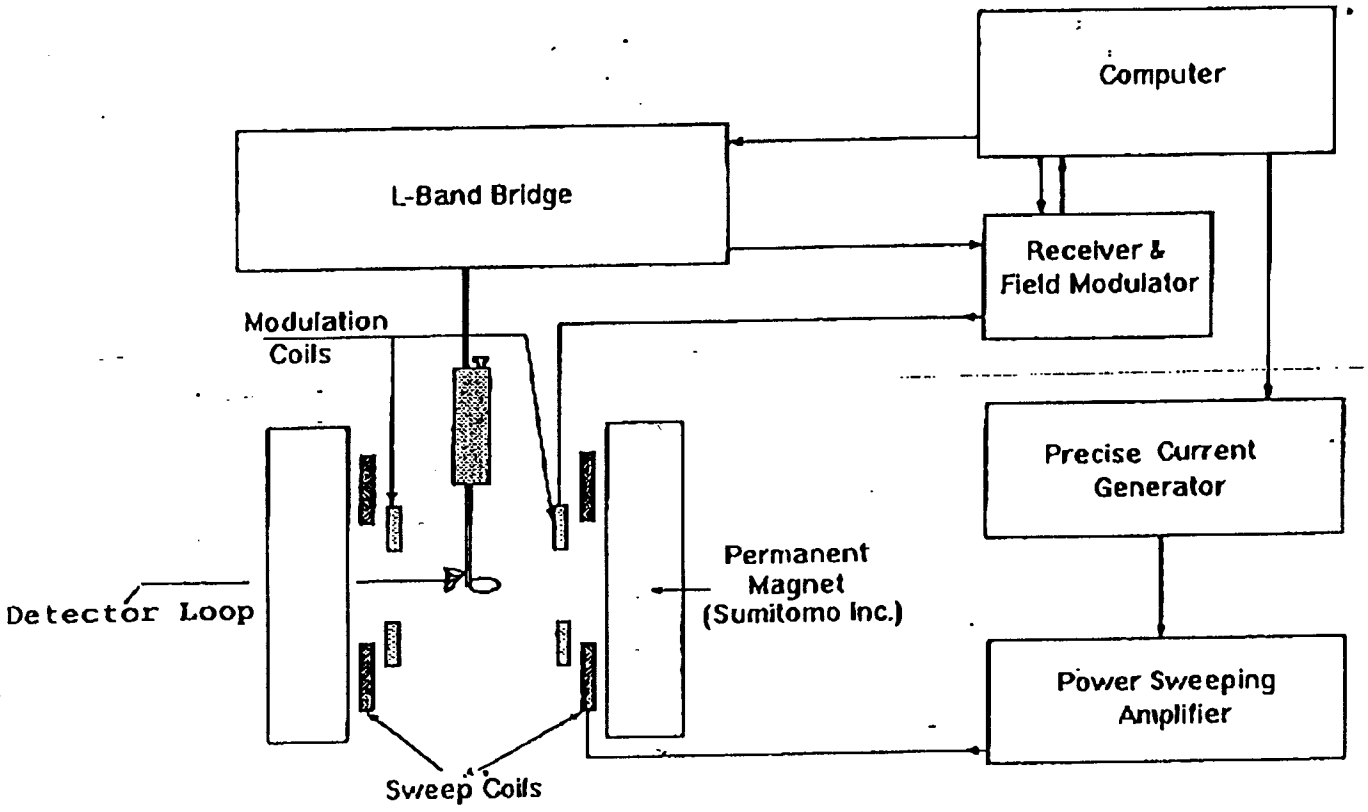


Picture 1



Picture 2

Fig. 2. Simplified Schematic Diagram of L-Band Spectrometer at Dartmouth College



3. The use of small solid inert particles (India ink, fusinite coal, or lithium phthalocyanine) as the oxygen sensitive paramagnetic species; and

4. The incorporation of detectors and control circuits which deal with the potential problems arising from carrying out EPR spectroscopy in a living animal with consequent large amounts of lossy materials and a variety of movements from physiological processes.

The existing instrument is not portable. During Phase 1, efforts habe been spent for converting the existing unit to a portable version. These efforts are described in the next section.

2.0 Phase 1 Accomplishments

2.1 Phase 1 Program Review

The original plan for the program was to design the instrument for battlefield conditions. On June 26, 95 a program review was held at the office of Col. William Wiesmann who is the Contracting Officer's Representative for the project. A decision was made at the meeting to develop the instrument for LSTAT (Life Support for Trauma and Transport) System rather than for the battlefield conditions. The main reason for the realignment of the program was the fact that the operation of the instrument in the battlefield would generate weak electromagnetic field which could provide the enemy the means of detecting and localizing the sites of operation. The following tasks were defined at the meeting:

1. Make a detailed analysis of the proposed alternative configurations for the magnet and the spectrometer, taking into account the size and the power possibilities and the constraints associated with the LSTAT concept. In particular, it now has become clear that our particular approach will be most valuable to military medicine by providing reading of p02 and other parameters in deep tissues through the use of placement of the sensing device via a needle, catheter, AND/OR positioning the detector intraoperatively.

2. The delineation of the appropriate configuration of the oxygen sensing probe in light of the altered circumstances in which the device will be operated. These include the possibilities of placing the needle probe selectively in the vascular system as well as in tissues. The needle type EPR resonator so far does not exist. Therefore, its design and constructions are very challenging.

3. Identification and development of configuration to the point that they can be immediately tested in animal in Phase 2 after completion of development of Phase 1. (This becomes especially important in view of the possibilities raised in our discussions with Col. Wiesmann, of carrying out some collaborative developments in the well characterized animal models that are actively being used at WRAIR.)

4. Delineation of the capabilities for the proposed configuration of the in vivo EPR instruments to measure pH, perfusion and nitric oxide. We also shall determine the feasibility of an alternative configuration to make measurements in limbs vs. the torso.

5. A related task will be to obtain more information about the characteristic of the LSTAT system and then to design the components of the instrument to be compatible with these characteristics. The key information to be obtained are the permissible range for:

A) The total weight of the EPR system
B) The available power
C) The dimensions of the magnet.

The following design efforts were completed during Phase 1 of the program:

o Source of Magnetic Field: Hemholtz Coil Design
o Surface Coil Design
o Needle/Catheter/Probe Design

2 .2 Source for Magnetic Field; Hemholtz Coil Design

Two basic approaches were considered. In many ways the simplest approach would be to obtain a permanent magnet with the required dimensions and homogeneity to make the desired measurements in a human limb. Our current knowledge of magnet technology does not indicate the availability of magnets with the required combination of size, homogeneity, and portability but we shall immediately undertake a systematic inquiry to magnet manufacturers as to the potential availability of such a magnet. To our knowledge the available magnets with the required features could be obtained with a 5" gap and magnetic field suitable for 1200 MHz operation (450 gauss) would weigh up to 150 pounds and therefore would not meet the requirements for portability. It is possible that there already exists technology that would overcome this problem.

Hemholtz Coil Design

We have designed a Helmholtz's coil as a potential source for the magnetic field. The cross section of the proposed coil is shown in Fig.3. The coil assembly is shown in Fig. 4. Helmholt coils are one of three alternative magnetic field sources (other sources, permanent magnet and electromagnet)

Advantages: small size, reduced weight.

Disadvantages: high power consumption .

For EPR L-band spectrometer operating a 1 GHz, the required magnetic field should be better than +/ 200mG within the sphere diameter of 10 mm. For Helmholtz coils, the magnetic field homogeneity is better than 0.1% within the sphere diameter = 0.17R, where R is the coil radius. To achieve the required homogeneity, the minimum coil radius should be 100mm. The magnetic field produced by a set of two Helmholtz coils is given by:

$$H(G) = (0.9)\, n\, (I/R$$

Fig 3

Helmholtz coil cross section

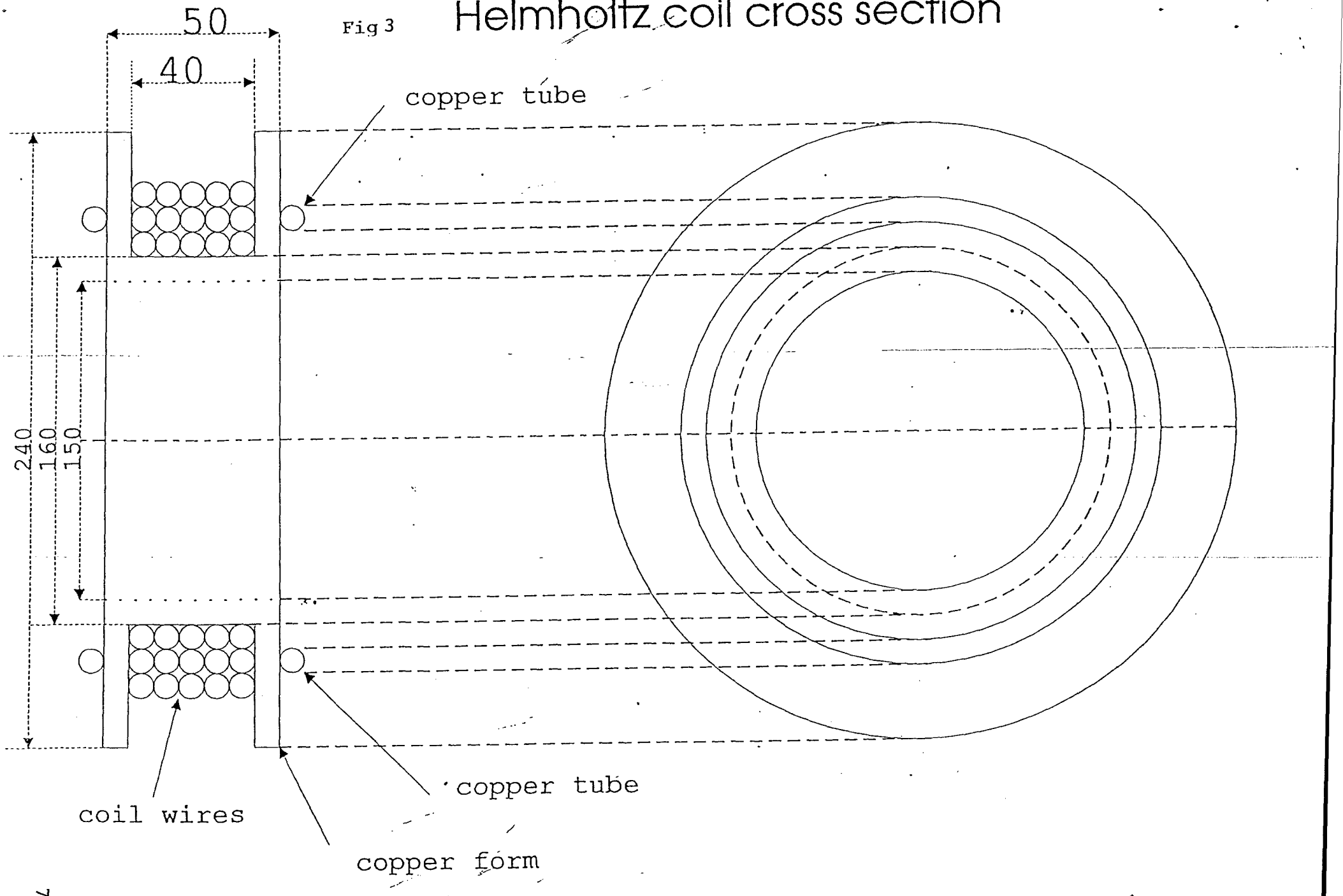
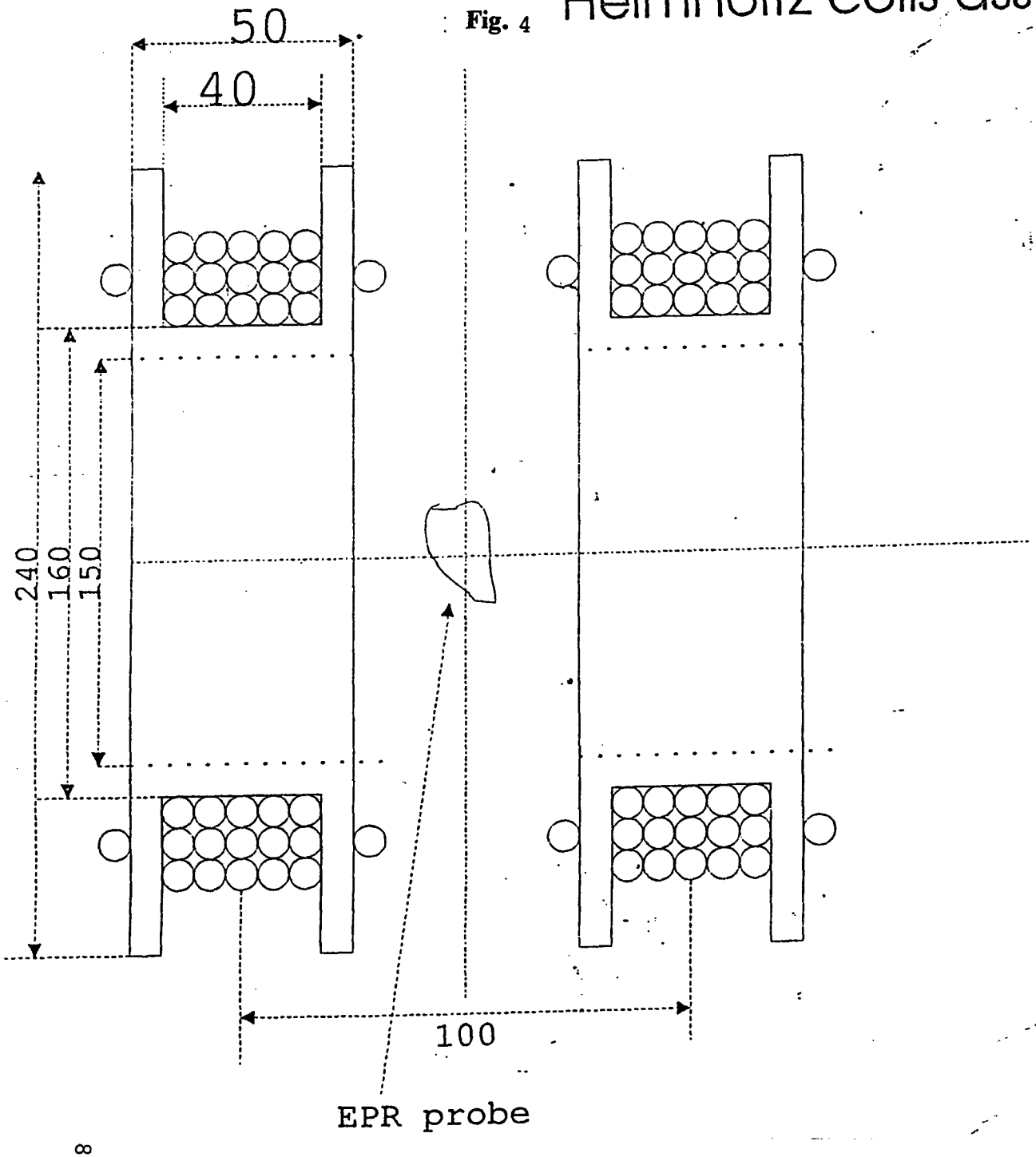


Fig. 4 Helmholtz coils assembly



where n = number of turns (each coil)
I= current (A)
R= coil radius (cm)

To obtain a magnetic field of 350 G, the product (n).(I) should be:
(n) (I) = 3850

The following design parameters have been selected:

Power supply voltage = 14-18 V

Cross section area of the magnet wire = 3.14 mm

Number of turns in each coil = 400

Resistance of each coil (@ room temp.) = 1.4

Current needed to produce the required magnetic field= (3850/400) = 9.6A

For a power supply voltage of 13.4 V, the power dissipation in each coil = 129W

The high power dissipation implies that the coil requires some type of cooling.

2.3 Surface Coil Design

A major part of this project is to minimize the size and weight of the systems subassemblies. However, there are still a lot of questions arising when considering a portable ESR spectrometer that cannot be answered without first performing characterization test experiments. One of subassembly component being initially examined is the development of a surface coil type resonator, to detect ESR signals from bigger sized biological objects.

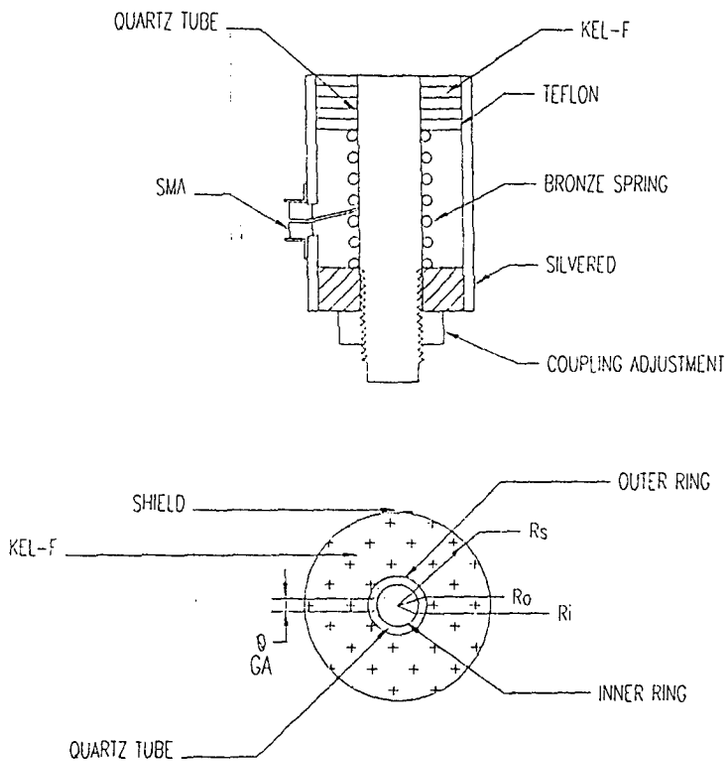
Two prototype surface-coils were assembled and are being tested:

1. Double split-ring resonator (Fig. 5)
2. External-loop resonator (Fig. 6 & 7)

The Double split rings resonator (diameter 12mm) enables detection of ESR signals from the depth of about 8 mm. The dependency of the signal intensity Vs distance in different mediums is shown in Figure 8.

The external loop in this design can possibly be modified to meet the specific needs of different measurement requirements. The maximum depth of detention depends on the loop diameter and shape, but it cannot exceed 10mm. Figure 9 shows the dependency of the signal's intensity Vs distance measured with 12mm diameter external loop design with different para-magnetic materials placed between ESR and loop plane.

Figure - 5 Double split-ring resonator



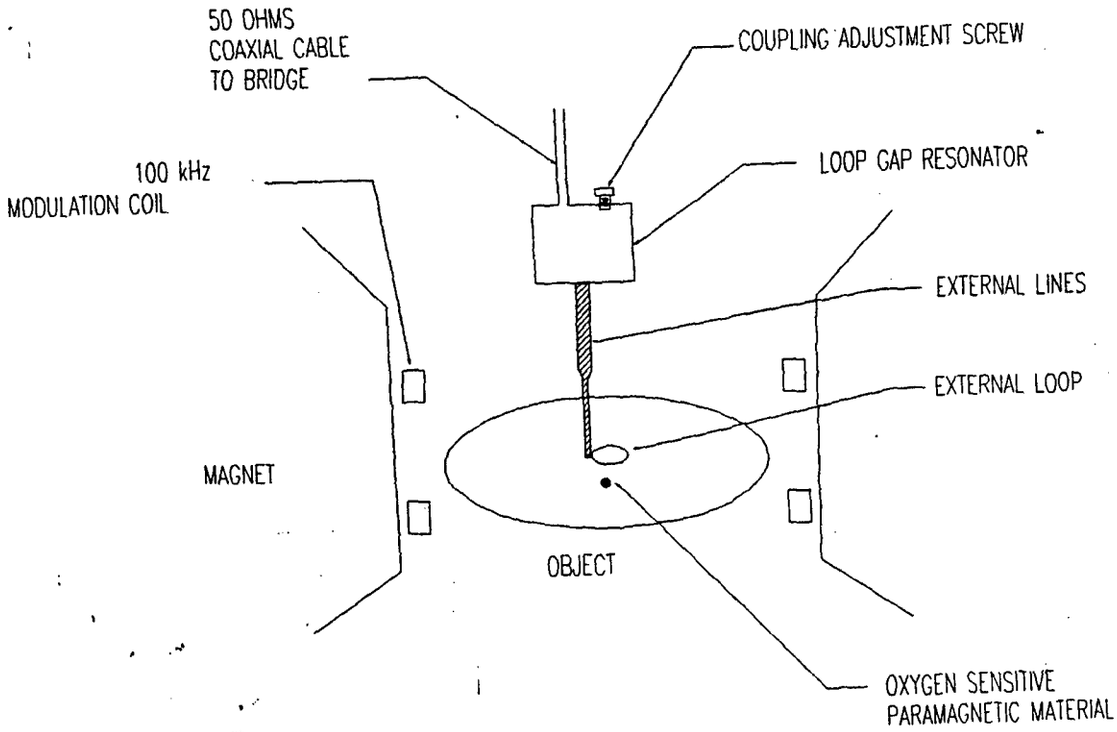


Figure 6 External-loop resonator

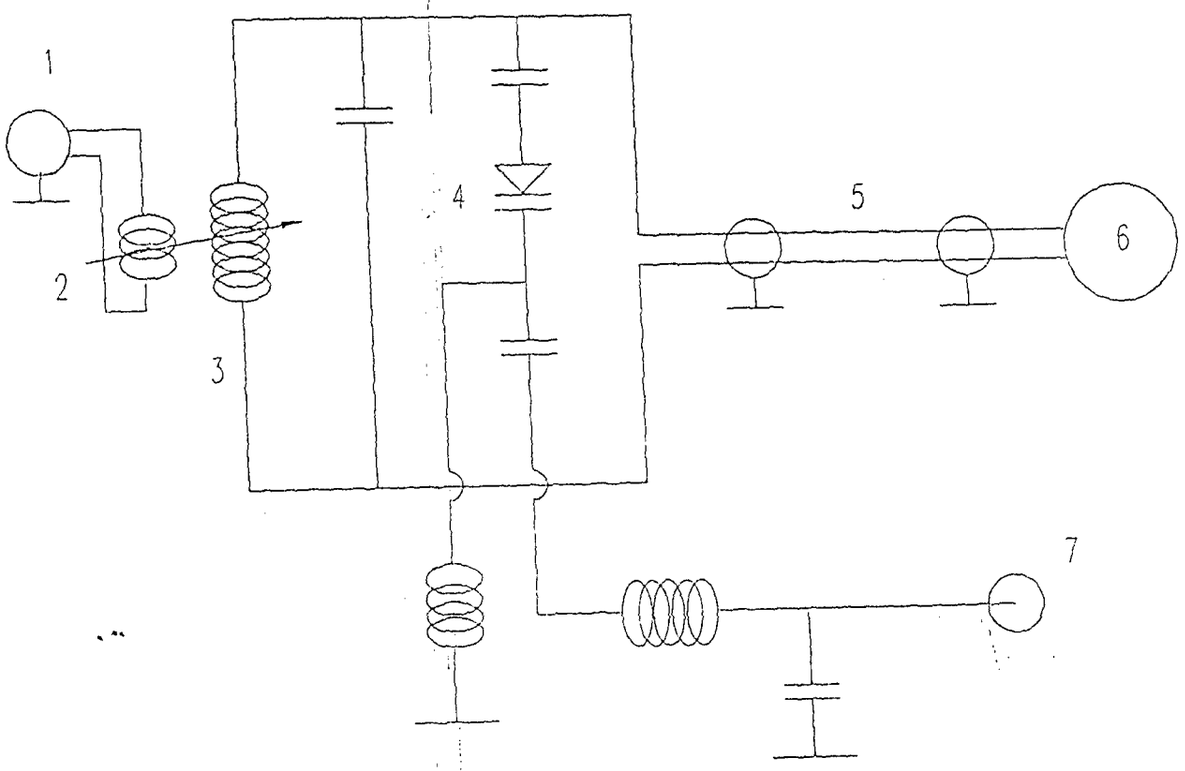


Figure - 7 Simplified Diagram of External Loop Resonator

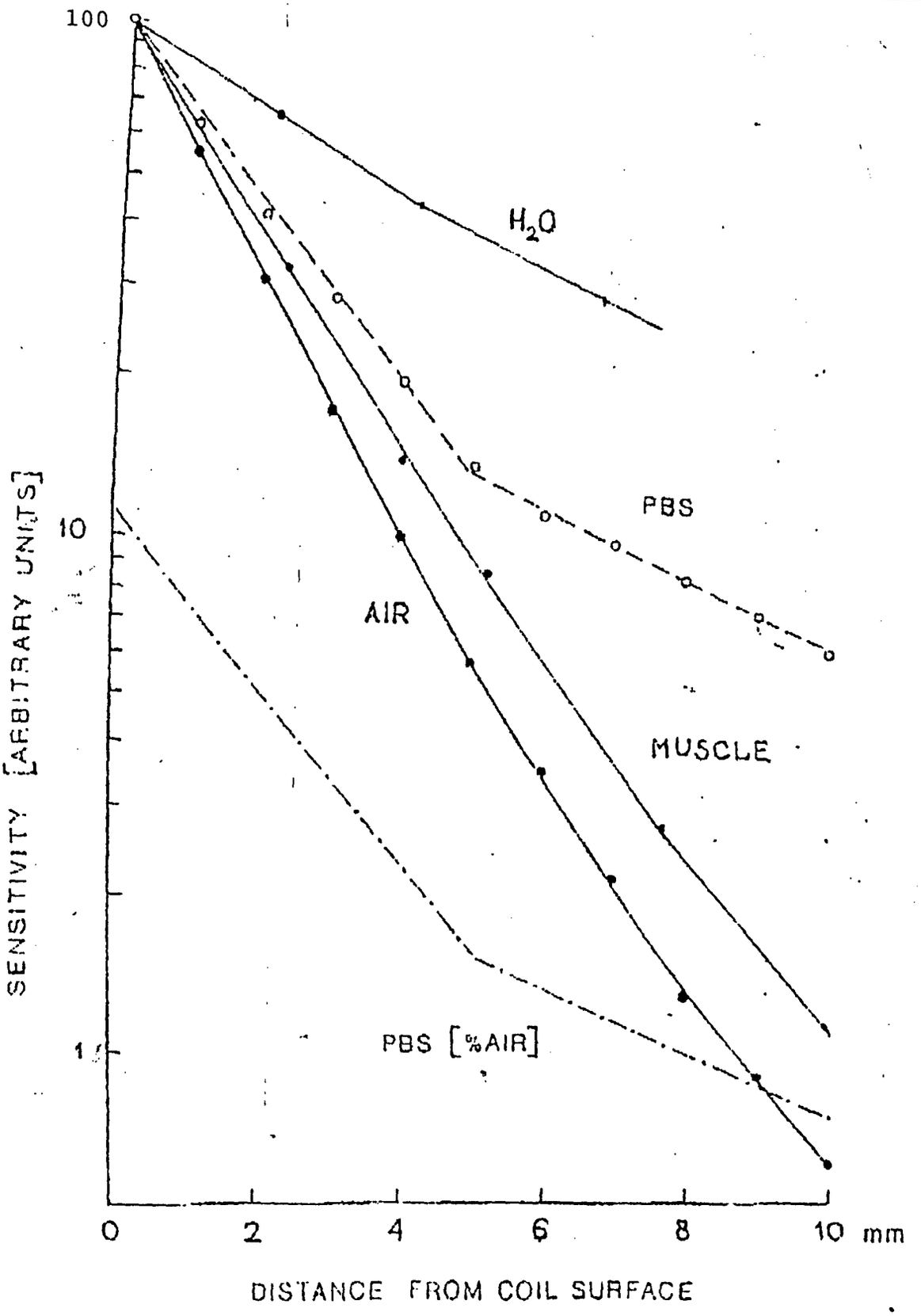


Fig. 8
Chart 1 - Sensitivity Vs Distance

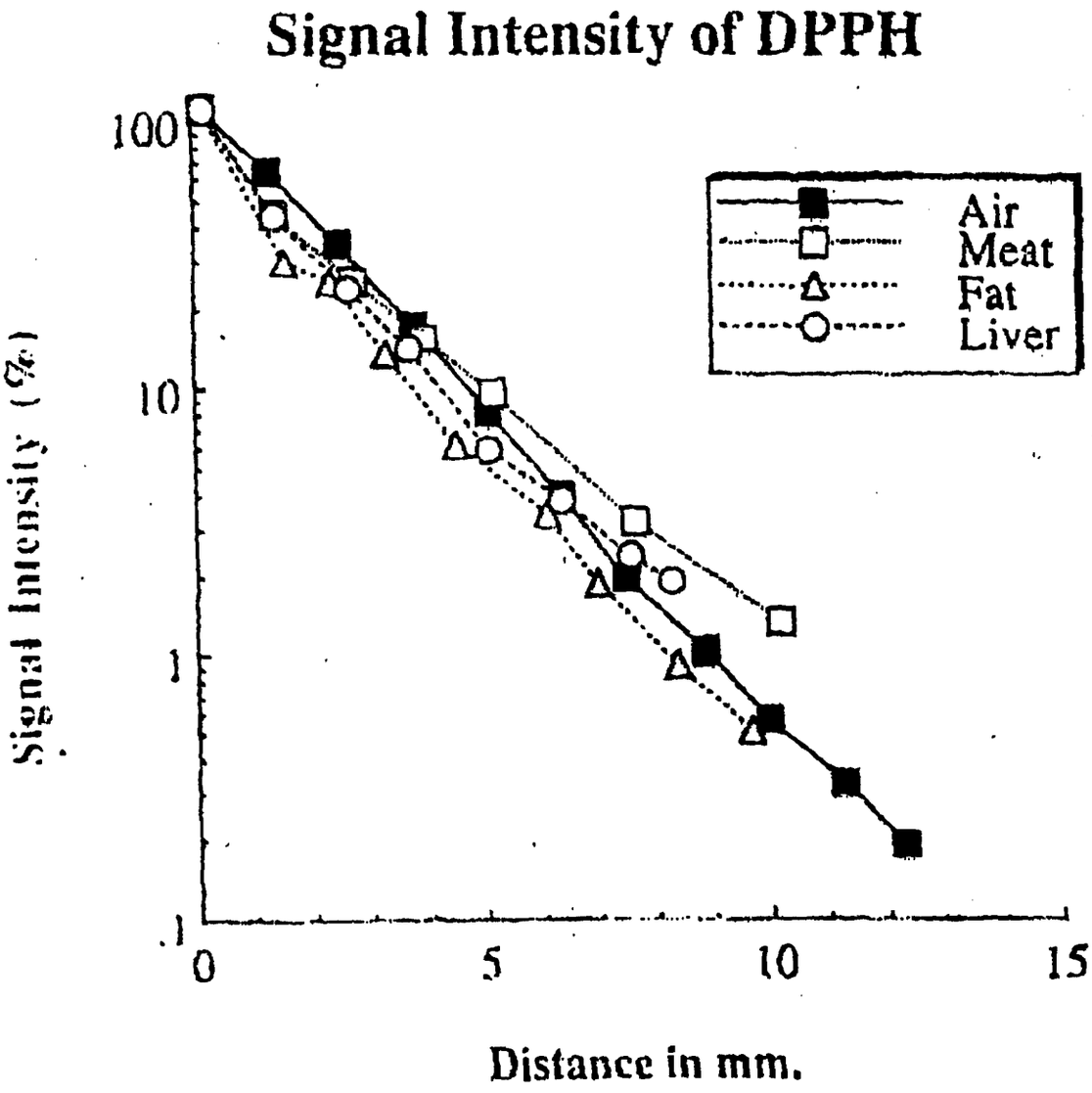
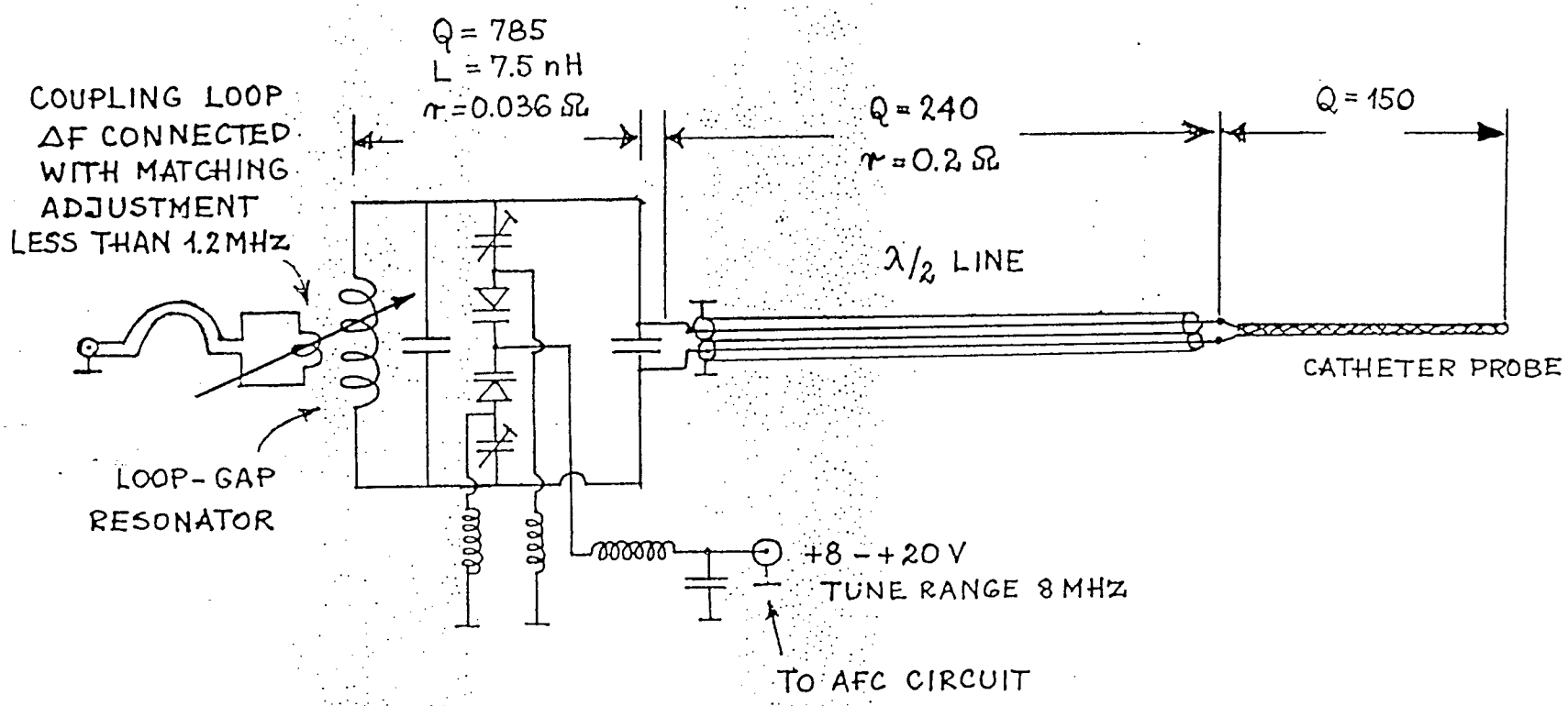


Fig. 9
Chart 2 - Signal Intensity of DPPH

2 .4 Design Needle/ Catheter Probe Design

A Needle/Catheter Probe was also designed for the spectrometer.
The design of the needle/catheter probe is based on a lambda/4 coaxial resonator principle. This configuration makes it possible to place the paramagnetic material inside a small loop mounted at the end of the lambda/4 coaxial line. Under resonance conditions the high frequency current, and consequently, B1 magnetic field, reach their maxima at the loop, providing a region of very high sensitivit-y. The open end of the lambda/4 resonator is connected with a high Q loop gap resonator via a low-loss lambda/2 transmission line. The application of the additional high-Q loop-gap resonator increases the Q-factor of the whole assembly and facilitates its precise coupling with a 50-ohm coaxial cable connecting the resonator with the microwave bridge. The resonator is electronically tuned with the use of varactor diodes. The schematic diagram of the whole system is shown in Fig. 10 and the cross-section of the needle resonator is shown in Fig. 11.

In preliminary experiments with the use of lithium phthalocyanine and fusinite placed optimally within the small loop, the signal-to-noise ratio with paramagnetic materials that were smaller than 0.5 x 0.5 mm was about 100 times better than that obtained with conventional resonators. The prototypes used so far are not sufficiently rigid to be inserted into tissues and cannot be submerged in liquids for an extended period of time, but the required developments are quite feasible.
The next steps in the development will be focused on:
1) obtaining suitable coatings for the paramagnetic materials which are stable, permeable to the material which is to be measured and sterilizable.
2) obtaining suitable construction materials which are sufficiently rigid, non magnetic and conducting. This microresonator.
3) reduce needle diameter to about 1mm.



SIMPLIFIED DIAGRAM

OF CATHETER PROBE ASSEMBLY

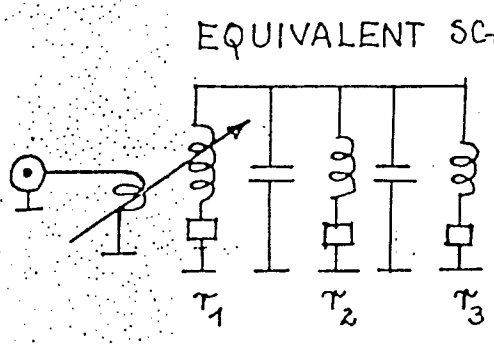
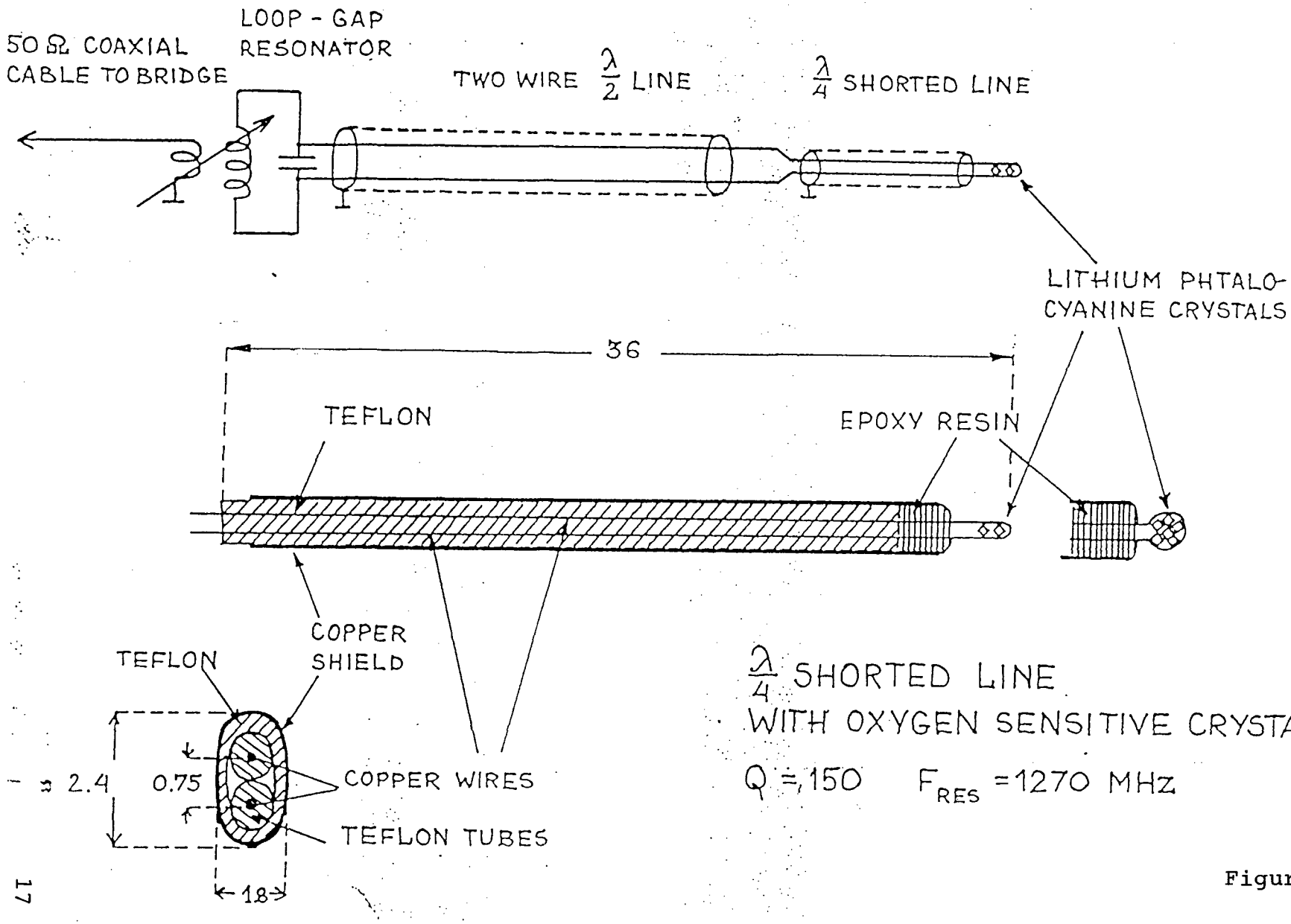


Figure 10

CROSS-SECTION OF CATHETER PROBE



$\frac{\lambda}{4}$ SHORTED LINE
WITH OXYGEN SENSITIVE CRYSTALS

$Q \doteq 150$ $F_{RES} = 1270$ MHz

Figure 11

3. Relationship with Future Research & Development

The design activities in Phase 1 will generate the information needed for a smooth and effective transition into Phase 2. It will provide a dependable and accurate means to measure the pO_2 rapidly and as often as required. It also will give the basis for a wide range of related uses in which the pO_2 can be measured with an accuracy and ease that has not been available previously.

4. Potential Applications

Military Application.

The proposed project is specifically designed to meet the criteria contained in the Solicitation by the Army.(A94-078). It should fully meet the criteria for battlefield use, after a successful transition from the pre-production prototype to a finished product in Phase 2. The technology is likely to be useful in a variety of settings for other military agencies as well in direct similarity to the uses for the army. Throughout the entire federal establishment this technology should have immediate use for federal and civilian emergency health care wherever such measurements would be useful.

Commercial Applications

It also should have significant use in non-emergency health care where tissue oxygenation is a concern for diagnosis, evaluation of status, or guiding therapy. Some of the immediate uses that are likely in this regard include evaluating and guiding care for peripheral vascular disease and for guiding tumor therapy, especially radiation therapy, by providing direct information on tissue oxygenation and its response to therapy. These types of data currently are not available by any non-invasive and repeatable means.

As indicated above, there could be widespread use in the health care system for clinical care on both an emergency and non emergency basis. The same technology also might have extensive feasibility for improving and replacing existing means to measure oxygen in the environment, in industrial processes, and in laboratories. Some of these uses would not necessarily require the portability feature but the product development associated with the developments for the Army should advance the feasibility of commercial development for other variants of the technology.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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PHYLIS M. RINEHART
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